Stereoselective Preparation of Cyclopropylmagnesium Reagents via a Br–Mg Exchange Using *i*-PrMgCl·LiCl in the Presence of Dioxane

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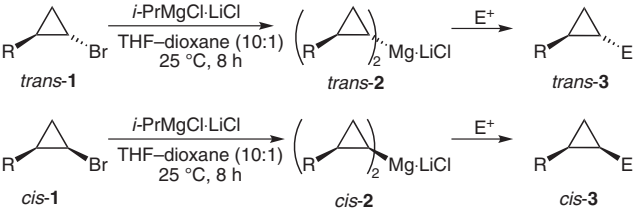
Abstract: The reaction of various cyclopropyl bromides with *i*-PrMgCl·LiCl in THF–dioxane provides the corresponding magnesiated cyclopropane reagents with complete retention of configuration.

Key words: Grignard reactions, organometallic reagents, stereoselectivity, copper, carbocycles

Organomagnesium reagents are key organometallic intermediates for organic synthesis.[1,2] They can be used efficiently for the functionalization of various cyclic systems.[3] Cyclopropanes are important ring systems displaying numerous interesting properties.[4] The stereoselective preparation of cyclopropyl organometallics is therefore an important synthetic target.[5] Whereas the standard preparation of these reagents is carried out through the direct insertion of magnesium into an organic halide,[6] this insertion into cyclopropyl halides is not stereoselective and provides an *E*/*Z* mixture of cyclopropylmagnesium reagents. Recently, we have reported that *i*-PrMgCl·LiCl allows the performance of a Br–Mg exchange with numerous aromatic and heteroaromatic bromides under exceedingly mild conditions.[7] Moreover, addition of 1,4-dioxane can additionally increase the rate of the exchange reaction.[8] Although the I–Mg exchange on cyclopropanes is known,[9] there is only one example for the Br–Mg exchange on the corresponding bromocyclopropanes.[10] Herein, we report a stereoselective synthesis of organometallic cyclopropyl building blocks. Thus, substituted cyclopropyl bromides of type **1** can be smoothly converted into the corresponding Grignard reagents **2** by using *i*-PrMgCl·LiCl in the presence of 1,4-dioxane or *s*-Bu_2Mg·LiCl.[8] The subsequent reaction with various electrophiles provides polyfunctionalized cyclopropanes of type **3** with good yields and excellent stereoselectivity (Scheme 1 and Table 1).

Thus, the reaction of *trans*-(2-bromocyclopropyl)benzene (**1a**) with *i*-PrMgCl·LiCl in a THF–dioxane (10:1) mixture at 25 °C produced the Grignard reagent **2a** within eight hours of reaction time. After addition of allyl bromide in the presence of CuCN·2LiCl[11] (5 mol%) the desired *trans*-disubstituted cyclopropane **3a** was isolated in 74% yield as a single stereoisomer (entry 1 of Table 1).



Scheme 1 Stereoselective Br–Mg exchange using *i*-PrMgCl·LiCl in THF–dioxane

Although the exchange reaction of bromocyclopropane **1a** with *sec*-Bu_2Mg·LiCl proceeds in the same manner, we have favored *i*-PrMgCl·LiCl which is commercially available.[12] However, by using *i*-PrMgCl·LiCl without the addition of 1,4-dioxane, the exchange reaction was sluggish and did not proceed to completion. The Cu(I)-mediated acylation of **2a** with benzoyl chloride furnished the cyclopropyl ketone **3b** in 72% yield (entry 2). The cyclopropyl thio derivative **3c** was obtained in 68% yield after reaction of **2a** with tetramethylthiuram disulfide[13] (25 °C, 2 h; entry 3 in Table 1). This opens new possibilities, since the dimethyldithiocarbamate moiety can easily be converted into various sulfur-containing products.[13] The corresponding *cis* isomer **2b** was also obtained after eight hours at 25 °C by the reaction of *cis*-(2-bromocyclopropyl)benzene (**1b**) with *i*-PrMgCl·LiCl in THF–dioxane. Cu(I)-catalyzed allylation and Cu(I)-mediated acylation led to the desired difunctionalized cyclopropanes **3d** and **3e** in 78% and 72% yields, respectively, as single stereoisomers (entries 4 and 5). A Br–Mg exchange reaction on 2-(*trans*-4-fluorophenyl)bromocyclopropane (**1c**) proceeded under the same conditions, and the resulting Grignard reagent **2c** displayed the same reactivity pattern as **2a** (entries 6–8). In all cases complete retention of configuration was observed. Similarly, the 1,1- and 1,2-diphenyl-substituted bromocyclopropanes **4** and **5** were converted into the corresponding magnesiated derivatives by reaction with *i*-PrMgCl·LiCl in THF–dioxane (Schemes 2 and 3).

Interestingly, for completion of the Br–Mg exchange reaction with 1-bromo-2,2-diphenylcyclopropane (**4**) two days at 25 °C were required, while *trans*-1,2-diphenyl derivative **5** was more reactive and the reaction proceeded cleanly in 16 hours at –16 °C (Schemes 2 and 3). In both cases, the resulting Grignard reagents were reacted with a standard set of electrophiles affording the desired trifunctionalized cyclopropanes **6a–f** and **7a–d** in 62–91% yield. Thus, the reaction with $MeSO_2SMe$ provided the thio-

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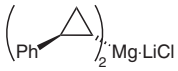
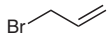
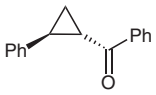
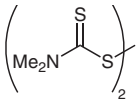
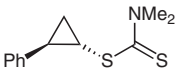
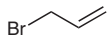
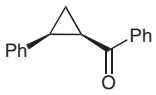
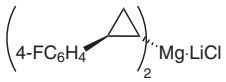
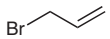
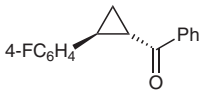
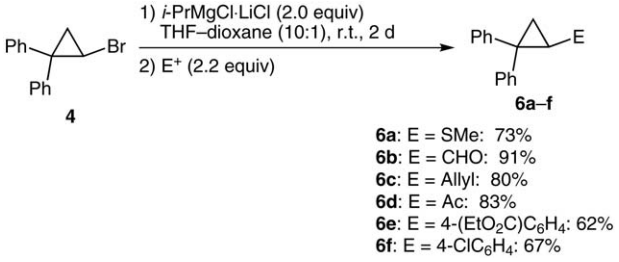
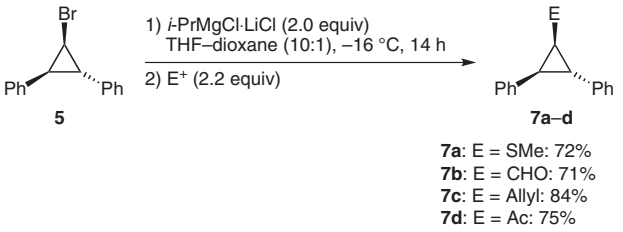
Table 1 Preparation and Reactions of Magnesiated Cyclopropanes of Type **2**

Entry	Grignard reagent	Electrophile	Product of type **3**	Yield (%)[a]
1	**2a** 		**3a** 	74[b]
2	**2a**	PhCOCl	**3b** 	72[c]
3	**2a**		**3c** 	68
4	**2b** 		**3d** 	78[b]
5	**2b**	PhCOCl	**3e** 	72[c]
6	**2c** 	DMF	**3f** 	89
7	**2c**		**3g** 	91[b]
8	**2c**	PhCOCl	**3h** 	76[c]

[a] Yield of analytically pure products.
[b] Yield after transmetalation using CuCN·2LiCl (5 mol%).
[c] Yield after transmetalation using CuCN·2LiCl (1.1 equiv).



Scheme 2 Br–Mg exchange and subsequent reaction with various electrophiles



Scheme 3 Br–Mg exchange and subsequent reaction with various electrophiles

methyl cyclopropanes **6a** and **7a**, while quenching with DMF led to the cyclopropyl aldehydes **6b** and **7b**. Successive addition of CuCN·2LiCl (5 mol% to 1.1 equiv) allowed us to perform an allylation with allyl bromide and an acylation with an acid chloride affording cyclopropanes **6c**,**d** and **7c**,**d** (Schemes 2 and 3). Transmetalation with zinc chloride (1.1 equiv, 1.0 M in THF) and Negishi cross-couplings[14] with an aryl iodide [$Pd(dba)_2$ (2 mol%), tfp (4 mol%)] and with an aryl bromide [$Pd(OAc)_2$ (1 mol%), S-Phos (1.5 mol%)] led to the aromatic products **6e**,**f** in 62–67% yield (Scheme 2).[15]

In summary, we have developed a stereoselective synthesis of functionalized cyclopropylmagnesium compounds starting from the corresponding cyclopropyl bromides using *i*-PrMgCl·LiCl in the presence of 1,4-dioxane.[16,17] Extensions of this work to polyfunctionalized cyclopropanes and their optically active analogues are currently underway in our laboratories.

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(16) **Typical Procedure for the Preparation of *trans*-(2-Allylcyclopropyl)benzene (3a) and *cis*-(2-Allylcyclopropyl)benzene (3b)**: A dry and argon-flushed 10-mL flask, equipped with a magnetic stirrer and a septum, was charged with *i*-PrMgCl·LiCl (1.1 M in THF, 1.1 mmol, 1.1 equiv) and 1,4-dioxane (0.1 mL). The *cis*- or *trans*-(2-bromocyclopropyl)benzene (**1a** or **1b**, 197 mg, 1.0 mmol, 1.0 equiv) was added neat at 25 °C. The resulting mixture was stirred at 25 °C for 8 h to complete the Br–Mg exchange (checked by GC–MS analysis of reaction aliquots). Allyl bromide (145 mg, 1.2 mmol, 1.2 equiv) followed by CuCN·2LiCl (1.0 M in THF, 0.01 mmol, 1.0 mol%) was added at 0 °C. The mixture was warmed to 25 °C and was quenched with a sat. aq NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$) and after filtration the solvent was removed in vacuo. Purification by flash chromatography (pentane, silica gel) yielded **3a** as a colorless oil [117 mg, 74% or **3d** (117 mg, 74%)].
Spectroscopic data for **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09–7.32 (m, 5 H), 5.96 (ddt, *J* = 16.6, 10.2, 6.3 Hz, 1 H), 5.02–5.17 (m, 2 H), 2.18–2.23 (m, 2 H), 1.70–1.73 (m, 1 H), 1.12–1.23 (m, 1 H), 0.83–1.00 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 137.7, 128.6, 126.1, 125.7, 115.4, 38.4, 23.2, 22.8, 16.1. IR (film): 3066 (m), 3002 (m), 1640 (m), 1607 (m), 1497 (m), 1030 (w), 996 (w), 912 (s), 753 (m), 696 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 158 (6), 118 (9), 117 (100), 116 (11), 115 (42), 104 (31), 103 (6), 91 (25), 78 (6), 77 (6). HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{14}$: 158.1096; found: 158.1082. Spectroscopic data for **3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.33 (m, 5 H), 5.80 (ddt, *J* = 16.5, 10.2, 6.3 Hz, 1 H), 4.91–5.03 (m, 2 H), 2.22 (ddd, *J* = 8.6, 8.6, 6.1 Hz, 1 H), 1.86–1.96 (m, 1 H), 1.69 (dddt, *J* = 15.5, 7.8, 6.4, 1.5 Hz, 1 H), 1.15–1.27 (m, 1 H), 1.01–1.09 (m, 1 H), 0.71–0.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6, 138.4, 129.6, 128.2, 126.0, 114.7, 33.2, 21.4, 18.3, 9.7. IR (film): 3066 (m), 3002 (m), 2908 (w), 1640 (m), 1604 (w), 1498 (m), 1028 (w), 911 (s), 769 (m), 727 (w), 698 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 158 (3) [M$^+$], 129 (11), 128 (10), 118 (10), 117 (100), 116 (11), 115 (41), 104 (37), 103 (9), 91 (24), 78 (8), 77 (8), 65 (5), 51 (5). HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{14}$: 158.1096; found: 158.1066.

(17) **Typical Procedure for the Preparation of 1-(2-Bromocyclopropyl)-4-fluorobenzene (1c)**:[15,18] A round-bottomed flask equipped with a magnetic stirrer was charged with 1-fluoro-4-vinylbenzene (6.11 g, 50.0 mmol), $CHBr_3$ (50.5 g, 0.20 mol), pinacol (0.768 g, 6.50 mmol) and triethylbenzylammonium chloride (0.569 g, 2.50 mmol). NaOH (8.00 g, 0.20 mol in 8 mL H_2O) was added dropwise and the reaction mixture was stirred vigorously for 16 h. Then, the solids were filtered off and washed with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic phases were dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure and the crude product was purified by distillation (100 °C, 2.5 mbar), furnishing 1-(2,2-dibromocyclopropyl)-4-fluorobenzene as a colorless liquid (10.2 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (t, *J* = 8.0 Hz, 1 H), 2.16 (dd, *J* = 10.5, 7.8 Hz, 1 H), 2.94 (dd, *J* = 10.2, 8.6 Hz, 1 H), 7.04–7.11 (m, 2 H), 7.22–7.28 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 (CH_2), 28.5, 35.6 (CH), 115.7 (d, *J* = 21.6 Hz, CH), 130.9 (d, *J* = 8.2 Hz, CH), 132.2 (d, *J* = 3.1 Hz), 162.6 (d, *J* = 246.7 Hz, CF). IR (film): 1606 (m), 1510 (vs), 1434 (w), 1228 (s), 1220 (s), 1158 (m), 1102 (m), 1052 (m), 1038 (m), 1014 (w), 926 (w), 860 (m), 830 (vs), 818 (s), 730 (m), 676 (s), 634 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 215 (24), 213 (26), 135 (8), 134 (100), 133 (88), 107 (7), 67 (12), 57 (6). HRMS (EI, 70 eV): *m*/*z* calcd for $C_9H_7{}^{79}Br_2F$: 291.8899; found: 291.8898.
A dry and argon-flushed two-necked Schlenk flask, equipped with a magnetic stirrer and a septum was charged with LiBr (3.02 g, 34.8 mmol). The salt was dried (0.01 mbar, 5 h, 150 °C) and then dissolved in THF (30 mL) and Et_2O (30 mL). The solution was cooled to –80 °C and *n*-BuLi (14.4 mL, 34.8 mmol, 2.42 M in hexane) was added, and the reaction mixture was cooled to –110 °C. 1-(2,2-Dibromocyclopropyl)-4-fluorobenzene (9.23 g, 31.6 mmol) was added dropwise and the reaction mixture was stirred for 1 h at –100 °C. Then, ethanol (15 mL) was added and the reaction mixture was warmed to 25 °C and was quenched with a sat. aq NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried

($MgSO_4$) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification (pentane, silica gel) furnished **1c** a colorless liquid (3.37 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.55 (m, 2 H), 2.34–2.41 (m, 1 H), 2.94–2.99 (m, 1 H), 6.94–7.05 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (CH_2), 21.3 (CH), 26.2 (CH), 115.3 (d, *J* = 21.3 Hz, CH), 127.5 (d, *J* = 8.3 Hz, CH), 135.3 (d, *J* = 3.2 Hz), 161.5 (d, *J* = 244.3 Hz, CF). IR (film): 1608 (w), 1600 (w), 1510 (vs), 1444 (w), 1226 (vs), 1180 (w), 1160 (m), 1104 (m), 1070 (w), 1042 (w), 1014 (w), 982 (w), 934 (m), 890 (m), 860 (m), 818 (vs), 718 (m), 702 (m), 634 (w), 612 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 136 (8), 135 (100), 134 (7), 133 (26), 115 (13), 109 (14), 107 (4), 83 (4), 67 (2), 56 (3). HRMS (EI, 70 eV): *m*/*z* calcd for $C_9H_8{}^{79}BrF$: 213.9793; found: 213.9777.

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